FLINT (A.) Jr.

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EXCRETORY FUNCTION OF THE LIVER.

BY

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PROFESSOR OF PHYSIOLOGY AND PHYSIOLOGICAL ANATOMY IN THE BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK.

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THE EXCRETORY FUNCTION OF THE LIVER.

I HAVE selected as the subject which I shall have the honor to present to the Section on Biology, the Excretory Function of the Liver, for the reason that it seemed to me better to discuss a question concerning which I had made personal and original investigations, than to recite the observations of others, however interesting and important the latter might be. I have ventured to assume that the views which I have to offer are not without importance; and they are certainly not so familiar as many other topics which I might with propriety have selected. I shall, therefore, endeavor to bring to your notice, in the simplest manner possible, what I have myself learned with regard to the liver as an organ of excretion.

It is now well known that the liver has a variety of important functions with which physiologists are more or less completely acquainted. It produces a substance which is converted into sugar and is carried away in the torrent of the circulation. It secretes bile, which performs an important office in digestion. In addition to the digestive function of the bile, I think I have shown that this fluid serves as the vehicle for the elimination of at least one excrementitious principle, which is discharged in a modified form in the feces. If the liver serve as an organ of excretion, it is evidently of great importance, from a pathological as well as a physiological point of view, that we should have an accurate knowledge of the mechanism of this function. For a long time, many pathological conditions have been attributed to defective or perverted action of the liver; still, the terms, "liver complaint," "biliousness," etc., have failed to convey any definite pathological notion, and it is probably true that the liver has been accused of numerous sins of omission and commission without any positive scientific reason. Many medical writers have assumed, in an indefinite way, that the liver possesses an excretory function; but, so far as I know, no physiologist had ever described any definite excrementitious substance eliminated by this organ prior to my observations in 1862.

There are certain general laws applicable to secretions and to excretions, which it is important to consider in discussing the probable functions of the bile:—

I. Secretions have some useful purpose to serve in the economy, and, as a rule, they are not discharged from the body in health. Excretions have no function in the economy and are discharged from the body.

II. The flow of secretions from the glands is usually intermittent, occurring when their function is called into action. The flow of excretions is usually either constant or remittent.

III. The production of excretions depends upon the general process of disassimilation, which is constant. The production of secretions has no

relation to disassimilation, but is connected with processes which usually take place at intervals.

IV. The elements of secretion, which give to secreted fluids their characteristic physiological properties, are formed *de novo* in the glands themselves out of materials furnished by the blood, and they do not pre-exist ready-formed in the circulating fluid. The elements of excretion pre-exist in the blood, being taken up by the lymph or by the blood from the tissues, and they are separated from the blood by organs which have no part in their actual production; except that excrementitious substances may be changed one into another, as creatine into creatinine, or uric acid into urea.

V. When secreting organs are removed or destroyed, there is no vicarious production of the peculiar elements of the secretions; these elements do not accumulate in the blood; and the system suffers simply from the absence of the function of the special secretion. When excreting organs are removed or destroyed, there may be a vicarious elimination of the excrementitious principles by other organs, or the system may suffer toxic effects from the accumulation of excrementitious matters in the circulating fluid.

VI. The characteristic elements of true secretions are generally reabsorbed by the blood; but they are taken up in a modified form, so that they are not to be recognized in the circulating fluid. Elements of excretion are with difficulty reabsorbed by the blood after they have once been separated by the proper organs.

The applications of the foregoing general laws may be readily made to the pancreatic juice as contrasted with the urine, which two fluids we may take as types respectively of secretions and of excretions. Before we make an application of these laws to the bile, we may consider the simple question as to whether it can be shown that this fluid has a useful function to perform as a secretion. If the bile have no such function, an animal would live and maintain its normal condition if the bile were diverted from the intestine and discharged from the body. This question has been made the subject of experimental observation by simply cutting off the bile-duct, and making a fistula into the gall-bladder, by which the bile is discharged. The operative procedure involved is not difficult, but is very apt to be followed by fatal peritonitis, so that few experiments of this kind have succeeded. In the experiments which have succeeded, in the hands of Schwann, Bidder and Schmidt, Nasse, Bernard, and myself, the dogs have lived for thirty or forty days, dying with all the symptoms of inanition. In one remarkably successful experiment performed by myself, the dog lived for thirty-eight days, had a voracious appetite, and died at the end of that period after having lost about four-tenths of his weight. In this experiment, the bile-duct was ligatured in two places, and the intermediate portion was exsected. A fistula was then made into the fundus of the gall-bladder, which was kept open. The animal ate well the very day of the operation, and there was very little peritonitis. The only observation in which contrary results were obtained is one made by Blondlot.[1] In this case, a fistula was made into the gall-bladder after the bile-duct had been divided. The animal lived for five years, and, after fifteen days following the operation, was in good flesh and apparently suffered no inconvenience from the discharge of the bile

[1] Blondlot, Essai sur les fonctions du foie et de ses annexes, Paris, 1846, page 55, *et seq.*; and Inutilité de la bile dans la digestion, Paris, 1851.

from the fistula. During the first fifteen days the animal licked the bile from the fistula, but this was afterward prevented by a muzzle. After a time he made no attempt to lick the bile. Blondlot attributed the emaciation which occurred during the first fifteen days to this licking of the bile. When the animal died, more than five years after the operation, an examination of the parts was made in the presence of several physicians and students of medicine, and no communication could be found between the bile-duct and the intestine. From this observation, Blondlot concluded that the bile had no function in digestion, and that it was a purely excrementitious fluid; and he assumed that the cause of death in other experiments of a similar kind was the licking of the bile as it flowed from the fistula. In my own case of biliary fistula, in which the dog died after thirty-eight days, the animal was prevented by a muzzle from licking the bile.

The only point to consider, as it seems to me, in this single experiment of Blondlot, is whether or not a communication had been re-established between the bile-duct and the intestine. If such a communication existed, it would be easy to explain the survival of the animal. The following experiment, which I undertook for a different purpose, satisfied me upon this point:—

I attempted to estimate, in a dog, the entire quantity of bile discharged in the twenty-four hours. With this object in view, I cut down upon the bile-duct, emptied the gall-bladder, secured a canula in the duct, and attached a rubber-bag to the canula, for the purpose of collecting the bile. Twenty-three hours after the operation, the bag was in place and nearly full of bile. Just before the end of the twenty-four hours, however, the animal ruptured the bag, and the experiment, as far as its original object was concerned, was a failure. I then simply pulled the canula from the wound and set the animal at liberty. In about four weeks, after the wound had closed and the feces had become of normal color, the animal, being in a perfectly normal condition, was killed, and the parts were carefully examined in the presence of several assistants. It is well known that, in dogs, ducts that have been divided have a remarkable tendency to become re-established. In this case, inasmuch as no bile was discharged externally, and the feces were of normal color, it was certain that the bile was discharged into the intestine. Nevertheless, I searched for more than an hour for the communication before it was discovered. The only reasonable way, as it appears to me, to reconcile the single experiment of Blondlot with those of other observers, is to suppose that, in his observation, a communication between the bile-duct and the intestine had become established, which he failed to find. The difficulty which I experienced in finding the communication in my own observation led me to conclude that a communication existed in the case reported by Blondlot, which he did not discover.

It is in accordance with my own observations, as well as with those of other physiologists, to conclude that the bile is a secretion, and that it has a function to perform in connection with the digestive process, which function is essential to life.

Assuming that the bile has an important and an essential office in digestion, is it not possible that it may also serve the purpose of elimination, and contain elements of excretion? This is a view which has not been advanced by physiologists, who have regarded the bile either as a secretion or an excretion, and have not imagined that it could serve both functions. Before I take up the experimental facts bearing upon this

question, I propose to consider the arguments to be drawn from a study of the composition of the bile, and its discharge into the intestine. It was this idea which first led me to investigate the physiological relations of cholesterine.

The bile certainly has an important function as a secretion; and its flow, although not intermittent, is more abundant during the process of intestinal digestion. The peculiar biliary salts (the glycocholate and the taurocholate of soda) are formed in the liver and do not pre-exist in the blood. When the structure of the liver is invaded by disease so as to interfere with the production of bile, the biliary salts do not accumulate in the blood. The biliary salts are reabsorbed in a modified form in the intestine; for the quantity of one of their elements (sulphur) found in the feces is very much less than the amount discharged into the intestine.

On the other hand, with regard to one constant constituent of the bile (cholesterine), we do not know that it has any function in connection with digestion. The secretion of bile is continuous, although its flow is increased during digestion. Cholesterine, while it is an invariable constituent of the bile, exists in the blood and in certain of the tissues of the body.

The questions to determine experimentally with regard to cholesterine are the following:—

Is cholesterine produced in any of the tissues of the body?

Is cholesterine separated from the blood by the liver?

When the liver undergoes structural change in disease, does cholesterine accumulate in the blood?

Is cholesterine reabsorbed in the intestine or is it discharged, either unchanged or in a modified form, in the feces?

These are the questions which I endeavored to answer by a series of experimental investigations, made in the spring of 1862, and published in October of the same year, in the American Journal of the Medical Sciences.

Process for the Estimation of Cholesterine in the Blood.—The following is the process which I fixed upon, after a number of trials, for the quantitative analysis of the blood for cholesterine: The entire blood, serum and clot, is evaporated to dryness. The dry residue is then pulverized in an agate mortar, and treated for from twelve to twenty-four hours with ether, in the proportion of about one fluidounce of ether to one hundred grains of the original weight of blood. This is filtered, and the ethereal extract, which contains cholesterine and fats, is evaporated. The residue of this evaporation is then extracted with boiling alcohol, in the proportion of one fluidrachm for one hundred grains of the original weight of blood. This extract is filtered while hot, and the filtrate is evaporated, leaving the cholesterine and a certain quantity of saponifiable fats. To remove the saponifiable fats, add to the residue a weak solution of potash, and allow it to remain for about two hours; then dilute with water, filter, and wash the filter with water until the liquid which passes through becomes neutral. Dry the filter; wash it with ether; evaporate the ether; extract the residue with hot alcohol as before; evaporate the alcoholic extract, and the residue will consist of cholesterine, perfectly pure, as can be determined by means of the microscope. Using this process for the determination of cholesterine, a number

of observations were made upon dogs, from which I select the following as typical, the results having been repeatedly confirmed.

OBS. I. *Experiment showing an Increase in Cholesterine in the Blood passing through the Brain.* (The dog was not etherized.)

Blood from the carotid, 140.847 grains, contained 0.108 grain of cholesterine, or 0.768 part of cholesterine per 1000.

Blood from the internal jugular, 97.811 grains, contained 0.092 grain of cholesterine, or 0.947 part of cholesterine per 1000.

The increase in the proportion of cholesterine in the blood in passing through the brain was 23.309 per cent.

This observation, which was frequently repeated with the same general result, seems to show that the blood gains cholesterine in its passage through the brain. It is well known that cholesterine is always present in nervous substance—not in a crystalline form, but in a state of molecular union with nitrogenized and other matters. In order to verify this fact, I examined the brains of two subjects who had been killed instantly by accident while in perfect health, in one case finding a proportion of cholesterine of 7.729 parts per 1000, and, in the other, 11.456 parts per 1000.

The experiment just detailed was made with a view of determining whether or not the brain gives up cholesterine to the blood as it circulates through this organ; and the following experiment was made to determine whether the venous blood of other parts contains an excess of cholesterine. Theoretically, the blood of the femoral vein should contain a little more cholesterine than arterial blood, this excess being derived from the nerves of the extremity, although the increase would probably be not so great as in the blood of the internal jugular, which comes almost exclusively from the great nervous centre.

OBS. II. *Experiment showing an Excess of Cholesterine in the Blood of the Internal Jugular and Femoral Veins over the Arterial Blood.* (The dog was not etherized.)

Blood from the carotid, 143.625 grains, contained 0.679 grain of cholesterine, or 0.967 part of cholesterine per 1000.

Blood from the internal jugular, 29.956 grains, contained 0.046 grain of cholesterine, or 1.545 part per 1000.

Blood from the femoral vein, 45.035 grains, contained 0.046 grain of cholesterine, or 1.028 part per 1000.

The increase in the proportion of cholesterine in the blood in passing through the brain was 59.772 per cent.

The increase in the proportion of cholesterine in the blood in passing through the lower extremity was 6.308 per cent.

This experiment confirms the previous observation upon the increase of cholesterine in the blood in passing through the brain, and it shows, in addition, that the blood gains cholesterine in other parts. Inasmuch as the nervous tissue is the only tissue in the extremities which contains cholesterine, it is probable that the excess contained in the blood of the femoral vein over the arterial blood was derived from the nerves.

It occurred to me that cases of old hemiplegia would present favorable conditions for verifying in the human subject the observations made on the lower animals. It has been ascertained that, when the function of nerves is permanently abolished, they soon become degenerated and their nutrition modified; and it seems probable that, if cholesterine be one

of their important products of disassimilation, the amount of cholesterine in the blood from paralyzed parts should be very small. Taking the blood, for example, from the paralyzed arm of a hemiplegic, this blood, coming from paralyzed parts, should contain less cholesterine than the blood from the sound arm. Of course, the blood from the arm contains no blood which has passed through the brain, which is assumed to be sound upon the paralyzed side. I examined, therefore, the blood from both arms in three cases of hemiplegia in the Charity Hospital on Blackwell's Island:—

Case I. Sarah Rumsby, æt. 47, is affected with hemiplegia of the left side. Two years ago she was taken with apoplexy and was insensible for three days. When she recovered consciousness she found herself paralyzed on the left side. She says she had epilepsy four or five years before the attack of apoplexy. She has now complete paralysis of motion on the affected side, with the exception of some slight power over the fingers. Sensation is not affected. The speech is perfect and her general health is good.

Case II. Anna Wilson, æt. 23, is affected with hemiplegia of the right side. Four months ago she became unconscious, and recovered in one day, with loss of motion and sensation on the right side. She is now improving and can use the right arm slightly. The leg is not so much improved because she will make no effort to use it.

Case III. Honora Sullivan, æt. 40, is affected with hemiplegia of the right side. About six months ago she became unconscious, recovering the next day with paralysis. The leg was less affected than the arm from the first. Her condition is about stationary as regards the arm, but the leg has somewhat improved.

A small quantity of blood was drawn from either arm in these three cases. In each instance it was drawn from the paralyzed side with difficulty, and but a small quantity could be obtained.

The specimens were all examined for cholesterine, with the following results:—

Obs. III. *Quantities of Cholesterine in the Blood of the Paralyzed and the Sound Sides in three cases of Hemiplegia.*

Cases.	Blood.	Choleste n	Cholesterine per 1000 parts.
	Grains.	Grains.	
Case I. Paralyzed side . . .	55.458	....	The watch-glass contained 0.031 grain of substance, but the most careful examination with the microscope failed to show crystals of cholesterine.
Sound side	128.407	0.062	0.481.
Case II. Paralyzed side . .	18.381	....	Same as Case I.
Sound side	66.396	0.062	0.808.
Case III. Paralyzed side . .	21.842	....	Same as Case I.
Sound side . . .	52.261	0.031	0.579.

The conclusion from the experiments upon dogs and the three observations upon the human subject is inevitable, that cholesterine is produced in the substance of the brain and in the nervous tissue generally, as this substance is not contained in the muscular tissue or in any other parts except the crystalline lens, the liver, and the spleen. The question now to determine is the relation of cholesterine to the nervous system. Is it

one of the products of disassimilation of its tissue? If this be the fact, cholesterine is an excrementitious product, and it must be separated from the blood by some organ or organs and discharged from the body. Inasmuch as the bile always contains cholesterine, we naturally look to the liver as the organ for its elimination; for it is not found in the product of any other gland.

I employed essentially the same method in studying the question of the elimination of cholesterine as that used in determining the seat of its production, analyzing the blood going to and coming from the liver. Upon this point I made a number of observations, the general results of which were invariable. The following experiment is a type of these observations:—

Obs. IV. *Experiment showing that Cholesterine is separated from the Blood in its Passage through the Liver.* (The dog was etherized.)

Arterial blood, 159.537 grains, contained 0.200 grain of cholesterine, or 1.257 part of cholesterine per 1000.

Blood of portal vein, 168.257 grains, contained 0.170 grain of cholesterine, or 1.009 part of cholesterine per 1000.

Blood of hepatic vein, 79.848 grains, contained 0.077 grain of cholesterine, or 0.964 part of cholesterine per 1000.

The loss in the proportion of cholesterine in arterial blood in passing through the liver was 23.309 per cent.

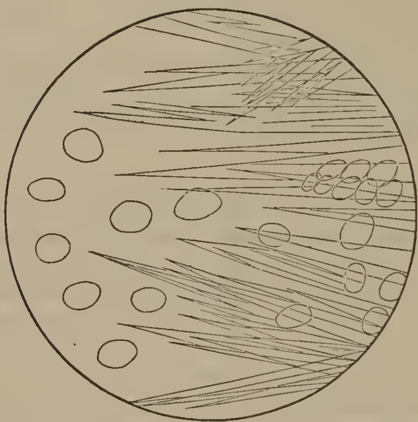
The loss in the proportion of cholesterine in the portal blood in passing through the liver was 4.460 per cent.

The bile always contains a certain proportion of cholesterine, which I found, in a specimen taken from the gall-bladder of a subject who had been killed instantly while in perfect health, to be 0.618 part per 1000. As I have demonstrated that the blood gains cholesterine in its passage through the brain and probably also from the general nervous tissue, that cholesterine is separated from the blood in its passage through the liver, and that cholesterine is invariably found in the bile and is discharged into the intestine, it seems to be proven that one of the functions of the liver is to eliminate this principle. If it can be shown that the cholesterine thus separated from the blood by the liver is discharged from the body, the fact that it is apparently produced in the nervous tissue and is taken up by the blood would point strongly to the conclusion that cholesterine is an excrementitious principle and is one of the products of disassimilation of the nervous matter.

Stercorine.—I made repeated examinations of the normal feces, with a view of determining the presence of cholesterine and its quantity. Although it is often stated by authors that cholesterine exists in the feces, I was unable to find it after the most careful examination, and I subsequently failed to discover any writer who had actually extracted it from the normal dejections. The process which I employed was essentially the same as that used in examinations of the blood, except that the extracts were decolorized by filtering through animal charcoal, and the alcoholic extract was treated with potash for one or two hours at nearly the boiling point. Treated in this way, the feces gave an extract which was non-saponifiable, but which did not crystallize for several days. It fused at a temperature of about 97° Fahr., while cholesterine fuses at 293°. After a few days, delicate, needle-shaped crystals began to appear, gradually increasing in number and breadth, and, as they became

broader, becoming split at the points and edges. These crystals presented all the characters of the crystals of a substance extracted from the serum of the blood by Boudet, in 1833 (Annales de Chimie et de Physique), which he called *séroline.* In some of my earlier observations upon the blood, I obtained these crystals; but I came to the conclusion that the so-called séroline was not a normal constituent of the blood, but was formed during the process used for the extraction of cholesterine. With this view, finding the so-called séroline a constant constituent of the normal feces, I called the substance stercorine, regarding it as one of the excrementitious principles of fecal matter. Crystals of stercorine are shown in the accompanying figure (Fig. 1). The rounded drops are probably composed of the same substance, as they disappear when the crystallization is complete. The idea that these crystals obtained from blood result from the transformation of cholesterine, is strengthened by the fact that the cholesterine of the bile is changed into stercorine in its passage through the alimentary canal. Stercorine, like cholesterine, is soluble in ether, very soluble in hot alcohol, and strikes a red color

Fig. 1.



Stercorine from normal human feces ($\frac{4}{10}$ inch objective).

with strong sulphuric acid. The points of distinction are the low fusing point and the form of the crystals.

I obtained from the feces of the twenty-four hours of a perfectly healthy man 10.417 grains of stercorine. It is estimated by Dalton that the total quantity of bile in twenty-four hours is 16,940.00 grains, and the total quantity of cholesterine, according to my estimate of 0.618 parts per 1000, is 10.469 grains, giving a difference between the estimated quantity of cholesterine and the actual quantity of stercorine extracted from the feces of only 0.052 of a grain. This sustains the idea of the change of the cholesterine of the bile into the stercorine of the feces.

Observations made by myself and others seem to show that the change of cholesterine into stercorine is incidental to the process of digestion. Cholesterine is found in quantity in the feces of hibernating animals and in the meconium, when, of course, there is no intestinal digestion, but when the bile is none the less discharged into the alimentary canal. I made an examination of human meconium and found cholesterine in the proportion of 6.245 parts per 1000, and no stercorine. I examined

the human feces in a case of simple jaundice from obstruction of the bile-duct, the feces being clay-colored, and found neither cholesterine nor stercorine. Nineteen days after, when the jaundice had disappeared and the color of the feces was normal, I found stercorine and no cholesterine. In the feces of a dog which had been deprived of food for forty-eight hours, I found stercorine and a small quantity of cholesterine. As far as can be learned from these facts and observations, then, it seems that the cholesterine of the bile is discharged in the feces unchanged when no digestion takes place, but that it is discharged in the form of stercorine under the ordinary and normal conditions of the digestive process.

Pathological Relations of Cholesterine; Cholesteræmia.—A knowledge of the relations of urea to nutrition bears so directly upon the pathology of renal diseases, that the pathological relations of any newly-discovered excrementitious principle assumes at once the greatest importance. If it be true that cholesterine, like urea, is a product of disassimilation, and that it is eliminated by the liver as urea is eliminated by the kidneys, we should expect to find, in cases of serious structural disease of the liver, an accumulation of cholesterine in the blood, or cholesteræmia, as we have uræmia in certain stages of extensive organic disease of the kidneys. It has long been observed, indeed, that, although simple jaundice due to resorption of the coloring matter of the bile is usually a trivial affection, there are cases of extensive change in the structure of the liver in which there is apparently a toxic condition dependent upon the presence of some excrementitious or poisonous substance in the blood. Pathologists have examined the blood in such cases with a view of ascertaining the nature of the supposed poisonous matter. Frerichs and others repeatedly examined the blood in cases of grave jaundice, expecting to discover the biliary salts or acids, but they never detected any substance which would react with Pettenkofer's test.[1] Becquerel and Rodier examined the blood in a case of jaundice and found "cholesterine excessively abundant," but they did not recognize the significance of this fact.[2] In such cases pathologists have looked for the biliary acids and their derivatives, and not for cholesterine. In order to throw some light upon the pathology of grave jaundice, Müller,[3] Kunde,[4] Lehmann,[5] and Moleschott[6] have extirpated the liver in frogs and kept the animals alive for several days, or even two or three weeks. On examining the blood, these physiologists failed to discover the biliary salts. They made no analyses of the blood for cholesterine. I hope to be able to show conclusively, by observations upon cases of disease of the liver in the human subject, that there may be an accumulation of cholesterine in the blood, or cholesteræmia, and that this occurs in certain cases of serious structural disease of the liver.

In cases of simple jaundice, there is resorption of the coloring matter of the bile from the excretory passages.

In cases of grave jaundice, which almost invariably terminate fatally, there is cholesteræmia, or accumulation of cholesterine in the blood.

1 Frerichs, Diseases of the Liver; New Sydenham Society, London, 1860, vol. i. p. 95.
2 Becquerel et Rodier, Traité de chimie pathologique; Paris, 1854, p. 210.
3 Müller, Manuel de Physiologie; Paris, 1851, tome i. p. 122.
4 Kunde, De Hepatis Extirpatione; Berolini, 1850.
5 Lehmann, Physiological Chemistry; Philadelphia, 1855, vol. i. p. 476.
6 Moleschott, Comptes Rendus; Paris, 1855, tome xl. p. 1040.

There are cases of structural disease of the liver, in which there is no jaundice, but nevertheless there is cholesteræmia.

In the following cases, having first determined the proportion of cholesterine in normal blood, I examined the blood for cholesterine with reference to the points just stated:—

OBS. V. *Proportion of Cholesterine in Normal Blood.*

Male, æt. 35 . .	0.445	part of cholesterine per 1000.
" " 22 . .	0.658	" " "
" " 24 . .	0.751	" " "

OBS. VI. *Case of Jaundice dependent probably upon Duodenitis.*—This case presented the symptoms of simple jaundice from temporary obstruction of the bile-duct. June 21, 1862, 212.428 grains of blood were taken from the arm. The proportion of cholesterine per 1000 was 0.508, which was within the limits of health, according to the results obtained in my examinations of normal blood. The feces, which were clay-colored, were examined, and I found neither cholesterine nor stercorine. July 11, the patient had entirely recovered; there was no jaundice; and the feces had become normal.

OBS. VII. *Case of Grave Jaundice with Cirrhosis.*—This case presented intense jaundice, ascites, great general prostration, and, toward the close of life, symptoms of blood-poisoning. The patient was admitted to the Charity Hospital on Blackwell's Island, June 16, 1862. On June 21, 50.776 grains of blood were taken from the arm. This blood contained a proportion of 1.850 part of cholesterine per 1000, an increase of 146.338 per cent. over the maximum quantity obtained from normal blood. The patient died June 27, 1862. There was double vision six days before death, and stupor for the last three or four days. The liver, examined after death, was in a condition of cirrhosis. The gall-bladder was contracted and contained but about two drachms of bile. The fibrous substance of the liver was increased in quantity, and the liver-cells were shrunken. The feces were taken a few days before death. The amount was small, only 272.1 grains in twenty-four hours, and contained 0.077 of a grain of stercorine. I found 10.417 grains of stercorine in the feces of the twenty-four hours in a healthy male.

OBS. VIII. *Case of Cirrhosis with Ascites and considerable affection of the General Health.*—In this case there was general prostration, confining the patient to the bed. After a tapping, the liver was explored and found to be considerably diminished in size. 117.193 grains of blood were taken from the arm, containing a proportion of 0.922 of a part of cholesterine per 1000, an increase of 22.769 per cent. over the maximum proportion obtained in my examinations of normal blood. In this case there were no nervous symptoms.

OBS. IX. *Case of Cirrhosis with Ascites and slight Constitutional Disturbance.*—This patient had suffered from ascites for eighteen months and had been tapped about thirty times. He is immediately relieved by tapping and goes out the next day. July 1, 1862, 251.567 grains of blood were taken from the arm, which gave a proportion of cholesterine of 0.246 of a part per 1000, or 44.719 per cent. less than the minimum obtained in my examinations of normal blood.

The cases just detailed, taken in connection with my observations upon animals, are certainly very striking. In the case of simple jaundice, which recovered, the proportion of cholesterine in the blood was within the limits of health. In the case of ascites, the patient not suffering much disturbance, the proportion of cholesterine in the blood was considerably below the normal standard. In the case of grave jaundice, which terminated fatally with symptoms of serious disturbance of the nervous system, the proportion of cholesterine in the blood was enor-

mously increased, being nearly three times greater than the maximum obtained in my examinations of normal blood. In the case of cirrhosis with considerable affection of the general health, the proportion of cholesterine in the blood was considerably above the maximum obtained in my examinations of normal blood.

Literature bearing upon the "New Excretory Function of the Liver," since the Publication of my Observations in 1862.

October, 1862.—My researches were published in the "American Journal of the Medical Sciences."

1868.—A translation of my memoir into French was published in Paris and presented to the Academy of Sciences for the Monthyon prize.

1869.—The commission from the French Academy of Sciences reported upon my observations and awarded an "honorable mention" with a "recompense" of fifteen hundred francs.

1869.—Grollemund (Thèse de Strasbourg) made observations upon the injection of the biliary salts into the blood in large quantity in dogs, and noted certain disturbances of the nervous system.

1869.—Tincelin (Thèse de Strasbourg) made observations in which he failed to obtain any marked nervous disturbances following the injection of the biliary salts into the blood in dogs.

1869.—Pagès (Thèse de Strasbourg) injected the bile-duct in dogs with a solution of sulphate of iron, which he thought destroyed the epithelium of the liver and interfered with its eliminative function, producing accumulation of cholesterine in the blood.

1870.—Feltz and Ritter (Journal de l'Anatomie, Paris, 1870) confirmed the results obtained by Pagès with the sulphate of iron. They found no marked effects following the injection of the biliary salts, taurine, or glycochol into the veins. They also injected cholesterine in soap and water. The cholesterine was not dissolved, and masses of cholesterine were found in the small pulmonary vessels, producing death by embolism.

1872.—Picot (Journal de l'Anatomie, Paris, 1872) noted an accumulation of cholesterine in the blood in a case of acute, yellow atrophy of the liver, which terminated fatally. He found a proportion of cholesterine in the blood in this case of 1.804 part per 1000, more than double the maximum which I obtained in examinations of normal blood.

1873.—Koloman Müller (Archiv für experimentelle Pathologie und Pharmakologie, Leipzig) made an elaborate series of experiments upon dogs. No serious or marked results followed the injection of the biliary salts or taurine into the blood. He rubbed cholesterine with glycerine and made a solution in soap and water. He injected 2.16 fluidounces of this solution, containing about 69 grains of cholesterine into the veins. In five experiments he produced "a complete picture of the symptoms of grave jaundice."

Conclusions of Koloman Müller.—"It appears to me to be certain that those cerebral symptoms which accompany severe jaundice and many diseases of the liver, the general manifestations of which have been called 'cholæmic intoxication,' are produced by an abnormal accumulation of cholesterine in the blood. This accumulation of cholesterine is contingent upon that alteration of the tissue of the liver, which, in such cases, it suffers more or less."

1875 and 1876.—Feltz and Ritter (Journal de l'Anatomie, Paris, 1875 and 1876) in opposition to their former experiments, conclude that the biliary salts injected into the blood produce grave changes, mainly in the blood corpuscles. The corpuscles become diffluent, change their form, the hæmaglobine transudes and crystallizes, and the power of absorption of oxygen progressively diminishes.

The general results of observations bearing upon the physiological relations of cholesterine, made since 1862, are confirmatory of my observa-

tions. As regards cholesteræmia, the experiments of Müller are the most important. Indeed, they supply the only missing link in my chain of experimental evidence; and they show conclusively that the symptoms of "grave jaundice," which I connected with cholesteræmia, may be produced by the artificial introduction of cholesterine into the circulation.

As an inevitable result of my observations, confirmed by others and extended by Koloman Müller, I can now confidently repeat the conclusions which I published in 1862.

Conclusions.—I. Cholesterine exists in the bile, the blood, the nervous matter, the crystalline lens, and the meconium, but does not exist in the feces in ordinary conditions. The quantity of cholesterine in the blood of the arm is from five to eight times more than the ordinary estimate.

II. Cholesterine is formed, in great part if not entirely, in the substance of the nervous matter, where it exists in great abundance, from which it is taken up by the blood, and constitutes one of the most important of the effete, or excrementitous products of the body. Its formation is constant, it always existing in the nervous matter and the circulating fluid.

III. Cholesterine is separated from the blood by the liver, appears as a constant element of the bile, and is discharged into the alimentary canal. The history of this substance, in the circulating fluid and in the bile, marks it as a product destined to be gotten rid of by the system, or an excretion. It pre-exists in the blood, subserves no useful purpose in the economy, is separated by the liver and not manufactured there, and, if this separation be interfered with, accumulates in the system, producing blood-poisoning.

IV. The bile has two separate and distinct functions dependent on the presence of two elements of an entirely different character. It has a function connected with nutrition. This is dependent on the presence of the glycocholate and taurocholate of soda, which do not pre-exist in the blood, subserve a useful purpose in the economy and are not discharged from it, are manufactured in the liver and peculiar to the bile, do not accumulate in the blood when the function of the liver is interfered with, and are, in short, products of secretion. But it has another function connected with depuration, which is dependent on the presence of cholesterine, which is an excretion. The flow of bile is remittent, being much increased during the digestive act, but produced during the intervals of digestion for the purpose of separating the cholesterine from the blood which is constantly receiving it.

V. The ordinary, normal feces do not contain cholesterine but contain stercorine (formerly called *séroline* from its being supposed to exist only in the serum of the blood), produced by a transformation of the cholesterine of the bile during the digestive act.

VI. The change of cholesterine into stercorine does not take place when digestion is arrested, or before this process commences; consequently, stercorine is not found in the meconium or in the feces of hibernating animals during their torpid condition. These matters contain cholesterine in large abundance, which also sometimes appears in the feces of animals after a prolonged fast. Stercorine is the form in which cholesterine is discharged from the body.

VII. The difference between the two forms of jaundice with which we are familiar, the one characterized only by yellowness of the skin and comparatively innocuous, while the other is attended with very grave symptoms and is almost invariably fatal, is dependent upon the obstruction

of the bile in the one case, and its suppression in the other. In the first instance, the bile is confined in the excretory passages and its coloring matter is absorbed, while, in the other, the cholesterine is retained in the blood and acts as a poison.

VIII. There is a condition of the blood dependent upon the accumulation of cholesterine, which I have called cholesteræmia. This occurs only when there is structural change in the liver, which incapacitates it from performing its excretory functions. It is characterized by symptoms of a grave character referable to the brain and dependent upon the poisonous effects of the retained cholesterine on this organ. It occurs with or without jaundice.

IX. Cholesteræmia does not occur in every instance of structural disease of the liver. Enough of the liver must be destroyed to prevent the due elimination of cholesterine. In cases in which the organ is but moderately affected, the sound portion is capable of performing the eliminative function of the whole.

X. In cases of simple jaundice, when the feces are decolorized and the bile is entirely shut off from the intestine, stercorine is not found in the evacuations; but in cases of jaundice with cholesteræmia, stercorine may be found, though always very much diminished in quantity, showing that there is an insufficiency in the separation of cholesterine from the blood, though its excretion is not entirely suspended. After death, but a small quantity of bile is found in the gall-bladder.